

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 1 031 556 A1

(12)

**EUROPEAN PATENT APPLICATION**

published in accordance with Art. 158(3) EPC

(43) Date of publication:

30.08.2000 Bulletin 2000/35

(51) Int. Cl.<sup>7</sup>: C07C 217/90, A61K 31/135

(21) Application number: 98947945.6

(86) International application number:  
PCT/JP98/04729

(22) Date of filing: 20.10.1998

(87) International publication number:  
WO 99/20598 (29.04.1999 Gazette 1999/17)

(84) Designated Contracting States:

AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU  
MC NL PT SE

• AIBE, Izumi,  
Taisho Pharmaceutical Co., Ltd  
Tokyo 170-8633 (JP)

(30) Priority: 20.10.1997 JP 28662397

• TAGUCHI, Minoru,  
Taisho Pharmaceutical Co., Ltd  
Tokyo 170-8633 (JP)

(71) Applicant:

TAISHO PHARMACEUTICAL CO. LTD  
Tokyo 170-8633 (JP)

• TOMISAWA, Kazuyuki,  
Taisho Pharmaceutical Co., Ltd  
Tokyo 170-8633 (JP)

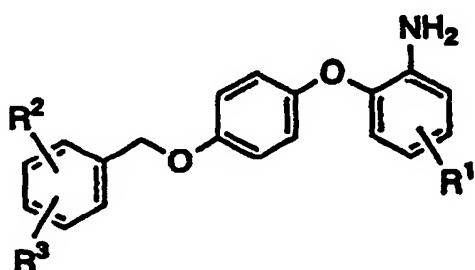
(72) Inventors:

- OTA, Tomomi,  
Taisho Pharmaceutical Co., Ltd  
Tokyo 170-8633 (JP)
- NAKANISHI, Misa,  
Taisho Pharmaceutical Co., Ltd  
Tokyo 170-8633 (JP)

(74) Representative: HOFFMANN - EITLE  
Patent- und Rechtsanwälte  
Arabellastrasse 4  
81925 München (DE)

(54) **2-PHENOXYANILINE DERIVATIVES**

(57) A 2-phenoxyaniline derivative represented by the formula:



wherein R<sup>1</sup> is a hydrogen atom or a lower alkoxy group, R<sup>2</sup> is a halogen atom or a nitro group, and R<sup>3</sup> is a hydrogen atom or a halogen atom, or a pharmaceutically acceptable salt thereof.

**Description****TECHNICAL FIELD**

5 [0001] The present invention relates to 2-phenoxyaniline derivatives having an inhibitory action on a  $\text{Na}^+/\text{Ca}^{2+}$  exchange system.

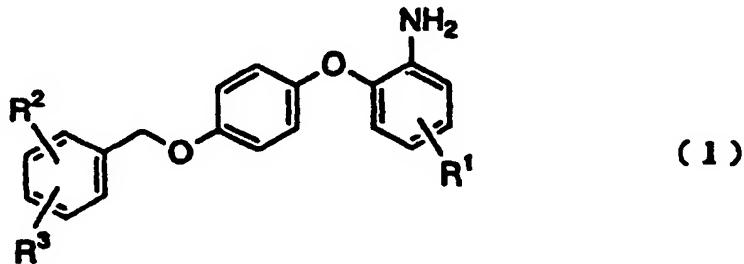
**BACKGROUND ART**

10 [0002] Among prior art compounds which inhibit a  $\text{Na}^+/\text{Ca}^{2+}$  exchange system selectively and prevent overload of  $\text{Ca}^{2+}$  in cells regarded as important in the cell injury mechanism after ischemia or reperfusion, there are known compounds as described in Japanese Patent Kokai 7-41465 and WO97/09306. However, there have not been known any compounds with a phenoxyaniline skeleton which have an inhibitory action on a  $\text{Na}^+/\text{Ca}^{2+}$  exchange system.

**DISCLOSURE OF THE INVENTION**

[0003] As a result of extensive researches on the compounds having an inhibitory action on a  $\text{Na}^+/\text{Ca}^{2+}$  exchange system, the present inventors have found that some kind of compounds having a phenoxyaniline skeleton meet said object, and the present invention has been accomplished based on the finding.

20 [0004] That is, the present invention is directed to a 2-phenoxyaniline derivative represented by Formula (1):



wherein  $R^1$  is a hydrogen atom or a lower alkoxy group,  $R^2$  is a halogen atom or a nitro group, and  $R^3$  is a hydrogen atom or a halogen atom, or a pharmaceutically acceptable salt thereof.

35 [0005] Furthermore, the present invention is directed to a pharmaceutical composition containing the above-mentioned compound or the pharmaceutically acceptable salt thereof as an effective component.

[0006] Furthermore, the present invention is directed to a pharmaceutical composition for the treatment or prevention of ischemic heart diseases, ischemic cerebral diseases or ischemic renal diseases containing the above-men-  
40 tioned compound or the pharmaceutically acceptable salt thereof as an effective component.

[0007] Furthermore, the present invention is directed to use of the above-mentioned compound or the pharmaceu-  
45 tically acceptable salt thereof for the manufacture of a pharmaceutical composition for the treatment or prevention of ischemic heart diseases, ischemic cerebral diseases or ischemic renal diseases.

[0008] Furthermore, the present invention is directed to a method for the treatment or prevention of ischemic heart  
45 diseases, ischemic cerebral diseases or ischemic renal diseases which includes the step of administering a pharmacologically effective amount of the above-mentioned compound or the pharmaceutically acceptable salt thereof to a human.

[0009] Furthermore, the present invention is directed to a pharmaceutical composition for the protection of cells  
50 during thrombolytic therapy, angioplasty, bypass operation of coronary artery or organ transplantation containing the above-mentioned compound or the pharmaceutically acceptable salt thereof as an effective component.

[0010] Furthermore, the present invention is directed to use of the above-mentioned compound or the pharmaceu-  
55 tically acceptable salt thereof for the manufacture of a pharmaceutical composition for the protection of cells during thrombolytic therapy, angioplasty, bypass operation of coronary artery or organ transplantation.

[0011] Furthermore, the present invention is directed to a method for the protection of cells during thrombolytic ther-  
55 apy, angioplasty, bypass operation of coronary artery or organ transplantation which includes the step of administering a pharmacologically effective amount of the above-mentioned compound or the pharmaceutically acceptable salt thereof to a human.

[0012] In the present invention, the lower alkoxy group refers to a straight or branched C<sub>1-6</sub> alkoxy group, and spe-

cific examples thereof are a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a sec-butoxy group, a tert-butoxy group, a pentyloxy group, an isopentyloxy group, a neopentyloxy group, a tert-pentyloxy group, a 1-methylbutoxy group, a 2-methylbutoxy group, a 1,2-dimethylpropoxy group, a hexyloxy group and an isohexyloxy group.

5 [0013] The halogen atom refers to a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

[0014] In the present invention, preferred phenoxyaniline derivatives are compounds of Formula (1) wherein R<sup>1</sup> is an ethoxy group or a propoxy group, in view of the inhibitory action on a Na<sup>+</sup>/Ca<sup>2+</sup> exchange system.

[0015] R<sup>2</sup> and R<sup>3</sup> are preferably the same or different, and are each a halogen atom, and more preferably a fluorine atom.

10 [0016] The compounds of the present invention can be prepared, for example, according to the following preparation scheme (wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above, X is a fluorine atom or a chlorine atom, and Y is a chlorine atom, a bromine atom or an iodine atom).

15

20

25

30

35

40

45

50

55

5

10

15

20

25

30

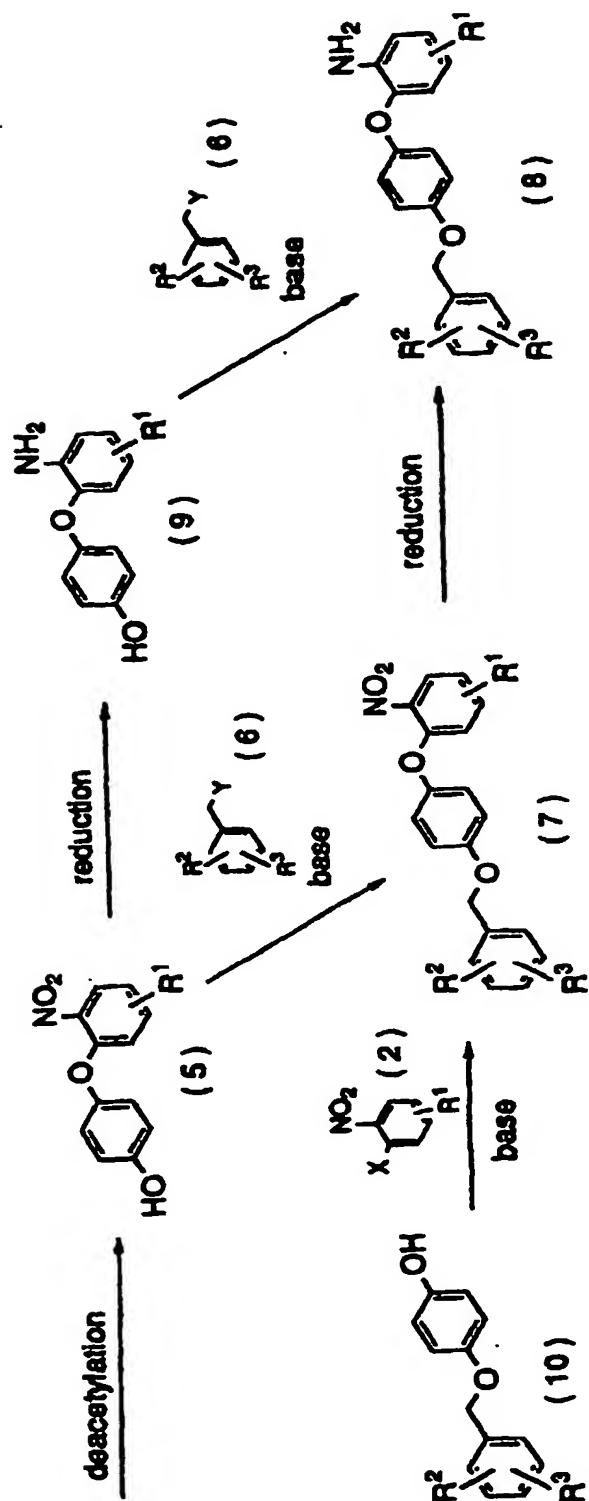
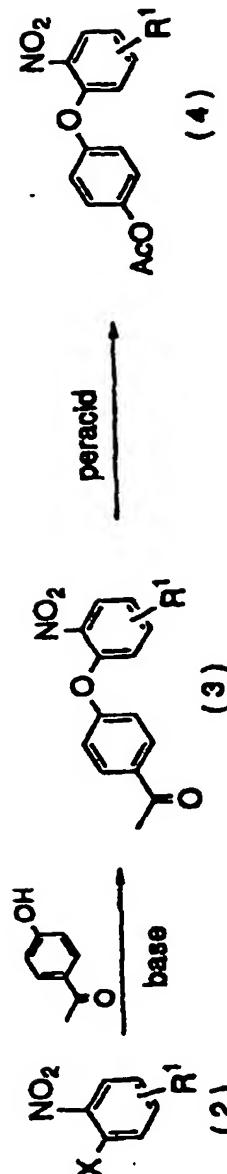
35

40

45

50

55



[0017] That is, a compound represented by Formula (2) and 4-hydroxyacetophenone are reacted in the presence of a base to give a compound represented by Formula (3).

[0018] Examples of the base to be used herein are organic and inorganic bases such as potassium tert-butoxide,

sodium hydroxide and sodium hydride. As a reaction solvent can be used N,N-dimethylformamide, tetrahydrofuran, etc. The reaction temperature is from room temperature to the reflux temperature.

[0019] Then, the compound represented by Formula (3) is reacted with a peracid to give a compound represented by Formula (4).

5 [0020] Examples of the peracid to be used herein are m-chloroperbenzoic acid and peracetic acid. As a reaction solvent can be used herein chloroform, methylene chloride, etc. The reaction temperature is from 0°C to room temperature.

[0021] The compound represented by Formula (4) is deacetylated in the presence of a base to give a compound represented by Formula (5).

10 [0022] Examples of the base to be used herein are sodium hydroxide, potassium hydroxide and potassium carbonate. As a reaction solvent can be used water, methanol, ethanol, etc., and they can be used alone or in admixture. The reaction temperature is preferably from 0°C to the reflux temperature.

[0023] The compound represented by Formula (5) is reacted with a compound represented by Formula (6) in the presence of a base to give a compound represented by Formula (7).

15 [0024] Examples of the base to be used herein are organic and inorganic bases such as potassium tert-butoxide, sodium hydroxide, sodium hydride and potassium carbonate. As a reaction solvent can be used acetone, N,N-dimethylformamide, tetrahydrofuran, etc. The reaction temperature is from room temperature to the reflux temperature.

[0025] The compound represented by Formula (7) is reduced to give a compound (8) of the present invention.

20 [0026] As a reducing agent can be used herein iron - ammonium chloride, iron - acetic acid, palladium carbon - hydrogen, lithium aluminum hydride, nickel chloride - sodium borohydride, etc. As a reaction solvent can be used herein water, methanol, ethanol, tetrahydrofuran, etc., and they can be used alone or in admixture. The reaction temperature is preferably from 0 °C to the reflux temperature.

25 [0027] Furthermore, if necessary, the compound represented by Formula (5) is reduced to give a compound represented by Formula (9), which is then reacted with the compound represented by Formula (6) in the presence of a base, thereby the compound of the present invention represented by Formula (8) can be obtained.

[0028] Examples of the base to be used herein are organic and inorganic bases such as potassium tert-butoxide, sodium hydroxide, sodium hydride and potassium carbonate. As a reaction solvent can be used herein acetone, N,N-dimethylformamide, tetrahydrofuran, etc. The reaction temperature is from room temperature to the reflux temperature.

30 [0029] If necessary, the compound (8) of the present invention can be also obtained by protecting the amino group of the compound represented by Formula (9) with an ordinary protective group such as a tert-butoxycarbonyl group and an acetyl group, and reacting the resulting compound with the compound represented by Formula (6), followed by deprotection.

[0030] Furthermore, the compound represented by Formula (7) can be also obtained by reacting a compound represented by Formula (10) with the compound represented by Formula (2) in the presence of a base.

35 [0031] Examples of the base to be used herein are organic and inorganic bases such as potassium tert-butoxide, sodium hydroxide and sodium hydride. As a reaction solvent can be used herein N,N-dimethylformamide, tetrahydrofuran, etc. The reaction temperature is from room temperature to the reflux temperature.

[0032] The compound represented by Formula (9) can be also prepared according to the following preparation scheme.

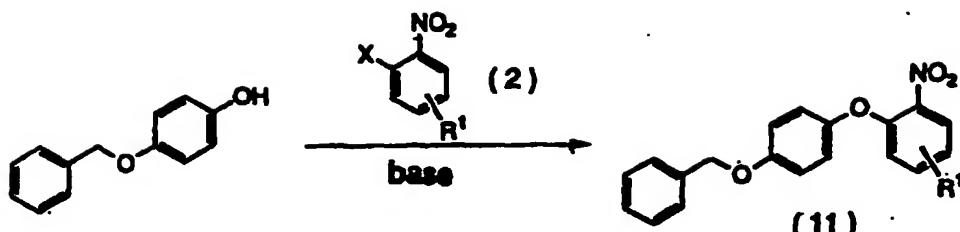
40

45

50

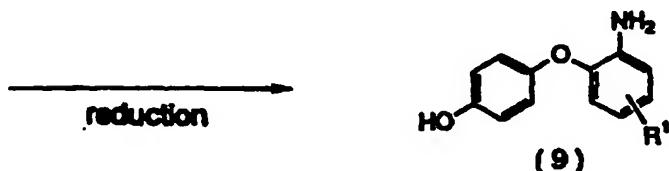
55

5



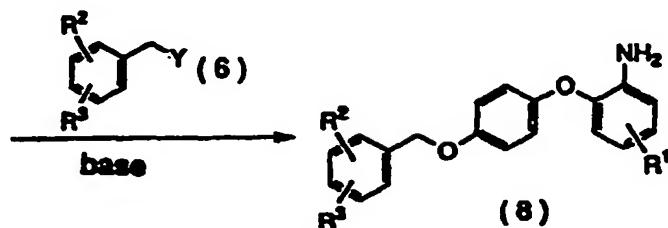
10

15



20

25



30

(wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $X$  and  $Y$  are as defined above).

[0033] That is, the compound represented by Formula (2) is reacted with 4-(benzyloxy)phenol in the presence of a base to give a compound represented by Formula (11).

[0034] Examples of the base to be used herein are organic and inorganic bases such as potassium tert-butoxide, sodium hydroxide and sodium hydride. As a reaction solvent can be used herein N,N-dimethylformamide, tetrahydrofuran, etc. The reaction temperature is from room temperature to the reflux temperature.

[0035] Then, the compound represented by Formula (11) is reduced to give the compound represented by Formula (9).

[0036] As a reducing agent can be used herein a metal catalyst such as palladium - carbon, platinum oxide, etc. under a hydrogen gas atmosphere. As a solvent can be used herein methanol, ethanol, acetic acid, etc., and if necessary, they are used as a mixture with N,N-dimethylformamide, tetrahydrofuran, etc. The reaction temperature is from 0°C to the reflux temperature.

[0037] The compound of the present invention can be administered orally or parenterally in appropriate dosage forms (tablets, pills, capsules, granules, dry-syrups, injectable preparations, etc.) which are prepared using appropriate known carriers and diluents.

[0038] The solid preparations can be produced by using various additives (e.g., a filler, a disintegrator, a binder, a lubricant, a coating agent, etc.) according to agitation granulation, fluidized bed granulation or disintegration granulation.

[0039] If necessary, an anti-oxidant, a coating agent, a coloring agent, a corrigent, a surface active agent, a plasticizer and others can be added.

[0040] The dose of the effective component of the pharmaceutical preparation according to the present invention can be varied depending on the age, body weight or administration route, but it is usually from 0.1 to 1000 mg/day to an adult, which can be administered in a single dose or divided doses.

## 55 INDUSTRIAL APPLICABILITY

[0041] The compounds of the present invention inhibit a  $\text{Na}^+/\text{Ca}^{2+}$  exchange system effectively, thus, they inhibit overload of  $\text{Ca}^{2+}$  in cells, prevent the cell injury after ischemia or reperfusion, are useful for the treatment or prevention

of ischemic heart diseases (e.g. myocardial infarction), ischemic cerebral diseases (e.g. cerebral infarction) or ischemic renal diseases, and further effective on the protection of cells during surgical treatments such as thrombolytic therapy, angioplasty, bypass operation of coronary artery and organ transplantation.

## 5 BEST MODE OF CARRYING OUT THE INVENTION

[0042] The present invention is illustrated in more detail by the following reference examples, examples and experiment. Furthermore, the structural formula of the compounds prepared in Examples 1 to 17 is shown in Table 1.

10

Table 1

Structural Formula				
Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	
1	H	3-F	4-F	hydrochloride
2	H	3-F	5-F	hydrochloride
3	H	2-F	3-F	hydrochloride
4	H	2-F	5-F	hydrochloride
5	H	2-F	6-F	hydrochloride
6	5-OCH <sub>2</sub> CH <sub>3</sub>	2-F	5-F	hydrochloride
7	5-OCH <sub>2</sub> CH <sub>3</sub>	2-F	6-F	hydrochloride
8	H	2-F	4-F	hydrochloride
9	5-OCH <sub>2</sub> CH <sub>3</sub>	3-F	H	-
10	5-OCH <sub>2</sub> CH <sub>3</sub>	2-F	3-F	hydrochloride
11	5-OCH <sub>2</sub> CH <sub>3</sub>	2-F	4-F	hydrochloride
12	5-OCH <sub>2</sub> CH <sub>3</sub>	3-F	4-F	hydrochloride
13	5-OCH <sub>2</sub> CH <sub>3</sub>	3-F	5-F	hydrochloride
14	5-OCH(CH <sub>3</sub> ) <sub>2</sub>	2-F	5-F	hydrochloride
15	H	3-NO <sub>2</sub>	H	hydrochloride
16	H	2-F	H	hydrochloride
17	H	2-Cl	5-Cl	hydrochloride

50

55

## Reference Example 1

4-(3,4-Difluorobenzyl)phenol

5 [0043]

(1) To a solution of 3,4-difluorobenzyl bromide (7.94 g, 38 mmol) and 4-hydroxyacetophenone (5.22 g, 38 mmol) in N,N-dimethylformamide (50 ml) was added potassium carbonate (6.00 g, 43 mmol), followed by stirring for 20 hours. The reaction solution was poured into water and extracted with ethyl acetate, and the organic layer was washed with water and a saturated aqueous sodium chloride solution and dried. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography [eluent; hexane - ethyl acetate (4:1)] to give 4-(3,4-difluorobenzyl)acetophenone (9.75 g).

15  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$ (ppm); 2.54 (s, 3H), 5.07 (s, 2H), 6.98 (d,  $J=9$  Hz, 2H), 7.10 - 7.33 (m, 3H), 7.94 (d,  $J=9$  Hz, 2H).

20 (2) To a solution of 4-(3,4-difluorobenzyl)acetophenone (9.03 g, 34.5 mmol) in chloroform (50 ml) was added m-chloroperbenzoic acid (5.95 g, 34.5 mmol), followed by stirring at room temperature for 20 hours. To the reaction solution was added m-chloroperbenzoic acid (1.07 g, 6.2 mmol), followed by stirring at room temperature for 3 days. The precipitated insoluble matter was removed by filtration, and the filtrate was washed with an aqueous sodium thiosulfate solution, an aqueous sodium bicarbonate solution, water and a saturated aqueous sodium chloride solution, successively, and dried. The solvent was evaporated under reduced pressure, and the resulting crude crystals were recrystallized from ethanol to give 4-(3,4-difluorobenzyl)phenyl acetate (6.97 g).

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  (ppm); 2.28 (s, 3H), 5.00 (s, 2H), 6.93 (d,  $J=9$  Hz, 2H), 7.02 (d,  $J=9$  Hz, 2H), 7.08 - 7.30 (m, 3H).

30 (3) To a solution of 4-(3,4-difluorobenzyl)phenyl acetate (6.77 g, 24.4 mmol) in methanol (100 ml) was added potassium carbonate (3.36 g, 24.3 mmol), followed by reflux for 3 hours. After allowing to stand overnight, the reaction solution was poured into water, made acidic with hydrochloric acid and extracted with chloroform. The solvent was evaporated under reduced pressure to give the title compound (5.68 g), which was used for the following reaction without purification.

35  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  (ppm); 4.54 (s, 1H), 4.94 (s, 2H), 6.75 (d,  $J=9$  Hz, 2H), 6.84 (d,  $J=9$  Hz, 2H), 7.06 - 7.29 (m, 3H).

[0044] The following compounds of Reference Examples 2 to 6 were synthesized in the same manner as in Reference Example 1.

40 Reference Example 2

4-(3,5-Difluorobenzyl)phenol

45 [0045]

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  (ppm); 4.45 (s, 1H), 4.99 (s, 2H), 6.68 - 6.88 (m, 5H), 6.95 (dd,  $J=2, 9$  Hz, 2H).

Reference Example 3

50 4-(2,3-Difluorobenzyl)phenol

[0046]

55  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  (ppm); 4.45 (bs, 1H), 5.09 (s, 2H), 6.76 (d,  $J=9$  Hz, 2H), 6.87 (d,  $J=9$  Hz, 2H), 7.03 - 7.33 (m, 3H).

## Reference Example 4

4-(2,5-Difluorobenzyl)phenol

5 [0047]

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz) δ (ppm); 4.58 (bs, 1H), 5.05 (s, 2H), 6.76 (d, J=9 Hz, 2H), 6.87 (d, J=9 Hz, 2H), 6.93 - 7.10 (m, 2H), 7.18 - 7.28 (m, 1H).

## 10 Reference Example 5

4-(2,6-Difluorobenzyl)phenol

15 [0048]

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz) δ (ppm); 4.62 (bs, 1H), 5.06 (s, 2H), 6.76 (d, J=9 Hz, 2H), 6.85 - 7.00 (m, 4H), 7.25 - 7.40 (m, 1H).

## 20 Reference Example 6

4-(2,4-Difluorobenzyl)phenol

25 [0049]

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz) δ (ppm); 4.51 (s, 1H), 5.01 (s, 2H), 6.72 - 6.95 (m, 6H), 7.46 (dt, J=6, 9 Hz, 1H).

## 30 Reference Example 7

4-(2-Nitrophenoxy)phenol

35 [0050]

(1) To a solution of 4-hydroxyacetophenone (5.44 g, 40 mmol) in N,N-dimethylformamide (70 ml) was added potassium tert-butoxide (4.48 g, 40 ml), followed by stirring for 30 minutes. Then, 1-fluoro-2-nitrobenzene (5.64 g, 40 mmol) was added, followed by stirring at 150°C for 8 hours. After allowing to stand overnight, the reaction solution was further stirred at 150°C for 6 hours, poured into water and extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution and dried. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent; chloroform) to give 4-(2-nitrophenoxy)acetophenone (7.41 g).

40

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz) δ (ppm); 2.59 (s, 3H), 7.04 (d, J=9 Hz, 2H), 7.18 (d, J=8 Hz, 1H), 7.35 (t, J=8 Hz, 1H), 7.63 (t, J=8 Hz, 1H), 7.99 (d, J=9 Hz, 2H), 8.04 (d, J=8 Hz, 1H).

(2) To a solution of 4-(2-nitrophenoxy)-acetophenone (7.14 g, 27.8 mmol) in methylene chloride (100 ml) was added m-chloroperbenzoic acid (5.27 g, 30.6 mmol), followed by stirring at room temperature for 48 hours. The reaction solution was diluted with chloroform, washed with an aqueous sodium thiosulfate solution, an aqueous sodium carbonate solution, water and a saturated aqueous sodium chloride solution, successively, and dried. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography [eluent; ethyl acetate - hexane (1:9)] to give 4-(2-nitrophenoxy)phenyl acetate (6.37 g).

50

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz) δ (ppm); 2.31 (s, 3H), 7.03 - 7.25 (m, 6H), 7.53 (t, J=8 Hz, 1H), 7.96 (d, J=8 Hz, 1H)

(3) To a solution of 4-(2-nitrophenoxy)phenyl acetate (6.32 g, 23.2 mmol) in methanol (100 ml) was added potassium carbonate (6.39 g, 46.3 mmol), followed by reflux for 3 hours. The reaction solution was poured into water, made acidic with hydrochloric acid and extracted with chloroform. The organic layer was washed with water and a saturated aqueous sodium chloride solution and dried. The solvent was evaporated under reduced pressure to give the title compound (5.35 g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz) δ (ppm); 4.98 (bs, 1H), 6.85 (d, J=9 Hz, 2H), 6.89 (d, J=8 Hz, 1H), 6.97 (d, J=9 Hz, 2H), 7.14 (t, J=8 Hz, 1H), 7.47 (t, J=8 Hz, 1H), 7.93 (d, J=8 Hz, 1H)

Reference Example 8

5

1-Chloro-4-ethoxy-2-nitrobenzene

[0051] To a solution of 4-chloro-3-nitrophenol (5.21 g, 30 mmol) in acetone (60 ml) were added ethyl iodide (5.94 g, 38 mmol) and potassium carbonate (4.53 g, 33 mmol), followed by stirring at 50°C for 5 hours. After allowing to stand overnight, the reaction solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution and dried, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [eluent; ethyl acetate - hexane (1:4)] to give the title compound (5.72 g).

15 m.p. 48 - 49.5°C.

Reference Example 9

1-Chloro-4-isopropoxy-2-nitrobenzene

20

[0052] The title compound was obtained from 4-chloro-3-nitrophenol and 2-iodopropane in the same manner as in Reference Example 8.

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz) δ (ppm); 1.35 (d, J=6 Hz, 6H), 4.56 (sext, J=6 Hz, 1H), 7.03 (dd, J=3, 9 Hz, 1H), 7.36 (d, J=3 Hz, 1H), 7.41 (d, J=9 Hz, 1H)

Reference Example 10

5-Ethoxy-2-(4-hydroxyphenoxy)aniline

30

[0053]

(1) To a solution of 4-(benzyloxy)phenol (5.68 g, 28.4 mmol) in N,N-dimethylformamide (100 ml) was added potassium tert-butoxide (3.50 g, 31.2 mmol), and after stirring for 10 minutes, 1-chloro-4-ethoxy-2-nitrobenzene (5.73 g, 28.4 mmol) was added to the reaction solution, followed by stirring at 150°C for 2 hours. The reaction solution was cooled to room temperature, poured into water and extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, and after drying, the solvent was evaporated under reduced pressure. The resulting crude crystals were recrystallized from methanol to give 4-[4-(benzyloxy)phenoxy]-3-nitrophenetole (7.18 g).

40

m.p. 96 - 96.5°C.

(2) To a solution of 4-[4-(benzyloxy)phenoxy]-3-nitrophenetole (4.26 g, 11.7 mmol) in a mixture of ethanol (70 ml) and tetrahydrofuran (50 ml) was added 10 % palladium - carbon (430 mg), followed by stirring under a hydrogen gas atmosphere at room temperature overnight. After removal of the insoluble matter by filtration, the solvent was evaporated under reduced pressure. The resulting crude crystals were recrystallized from a mixture of ethyl acetate and hexane (1:9) to give the title compound (2.63 g).

50 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 200 MHz) δ (ppm); 1.30 (t, J=6 Hz, 3H), 3.90 (q, J=6 Hz, 2H), 4.80 (bs, 2H), 6.05 (dd, J=2, 8 Hz, 1H), 6.35 (d, J=2 Hz, 1H), 6.60 (d, J=8 Hz, 1H), 6.65 - 6.77 (m, 4H), 9.05 (s, 1H)

Reference Example 11

55

2- 4-(Hydroxyphenoxy)-5-methoxyaniline

[0054] The title compound was obtained from 4-(benzyloxy)phenol and 4-chloro-3-nitroanisole in the same manner as in Reference Example 10.

m.p. 105 - 106°C.

Reference Example 12

5    2- 4-(Hydroxyphenoxy)aniline

[0055]    The title compound was obtained from 4-(benzyloxy)phenol and 1-fluoro-2-nitrobenzene in the same manner as in Reference Example 10.

10    <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 200 MHz) δ (ppm); 4.84 (s, 2H), 6.48 (dt, J=2, 8 Hz, 1H), 6.63 (dd, J=2, 8 Hz, 1H), 6.67 - 6.87 (m, 6H), 9.16 (s, 1H)

Example 1

15    2-[4-(3,4-Difluorobenzyloxy)phenoxy]aniline hydrochloride

[0056]

20    (1) To a solution of 4-(3,4-difluorobenzyloxy)phenol (1.00 g, 4.2 mmol) in N,N-dimethylformamide (20 ml) was added potassium tert-butoxide (0.47 g, 4.2 mmol), followed by stirring at room temperature for 30 minutes. To the reaction solution was added 1-fluoro-2-nitrobenzene (0.60 g, 4.3 mmol), followed by stirring at 150°C for 5 hours. After allowing to stand overnight, the reaction solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution and dried. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent; chloroform) to give 1-[4-(3,4-difluorobenzyloxy)phenoxy]-2-nitrobenzene (1.41 g).

m.p. 74 - 75°C.

30    (2) To a solution of 1-[4-(3,4-difluorobenzyloxy)phenoxy]-2-nitrobenzene (0.96 g, 2.7 mmol) in ethanol (50 ml) were an iron powder (0.75 g, 13.4 mg-atom) and a solution of ammonium chloride (0.09 g, 1.7 mmol) in water (10 ml), followed by reflux for 3 hours. The reaction solution was cooled to room temperature, and after removal of the insoluble matter by filtration, the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and dried over magnesium sulfate. After removal of the drying agent, 4 N hydrogen chloride - ethyl acetate solution (2 ml) was added, followed by stirring for 30 minutes. The precipitated crystals were collected by filtration and dried to give the title compound (0.92 g).

m.p. 195 - 196°C.

[0057]    The following compounds of Examples 2 to 14 were synthesized in the same manner as in Example 1.

40    Example 2

2-[4-(3,5-Difluorobenzyloxy)phenoxy]aniline hydrochloride

45    [0058]

m.p. 174.5 - 176.5°C.

Example 3

50    2-[4-(2,3-Difluorobenzyloxy)phenoxy]aniline hydrochloride

[0059]

55    m.p. 178.5 - 179.5°C.

## Example 4

2-[4-(2,5-Difluorobenzyl)phenoxy]aniline hydrochloride

5 [0060]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 200 MHz) δ (ppm); 5.13 (s, 2H), 6.78 (dd, J=2, 8 Hz, 1H), 7.03 - 7.18 (m, 6H), 7.25 - 7.50 (m, 4H)

## 10 Example 5

2-[4-(2,6-Difluorobenzyl)phenoxy]aniline hydrochloride

15 [0061]

m.p. 163.6 - 166.4°C.

## Example 6

20 2-[4-(2,5-Difluorobenzyl)phenoxy]-5-ethoxyaniline hydrochloride

[0062]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 200 MHz) δ (ppm); 1.31 (t, J=7.0 Hz, 3H), 3.96 (q, J=7.0 Hz, 2H), 5.10 (s, 2H), 6.38 - 7.50 (m, 10H)

## Example 7

2-[4-(2,6-Difluorobenzyl)phenoxy]-5-ethoxyaniline hydrochloride

30 [0063]

m.p. 199 - 200.5°C.

## 35 Example 8

2-[4-(2,4-Difluorobenzyl)phenoxy]aniline hydrochloride

40 [0064]

m.p. 181.5 - 183°C.

## Example 9

45 5-Ethoxy-2-[4-(3-fluorobenzyl)phenoxy]aniline

[0065]

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz) δ (ppm); 1.39 (t, J=7.0 Hz, 3H), 3.77 (brs, 2H), 3.98 (q, J=7.0 Hz, 2H), 5.02 (s, 2H), 6.25 (dd, J=2.9, 8.8 Hz, 1H), 6.37 (d, J=2.9 Hz, 1H), 6.77 (d, J=8.8 Hz, 1H), 6.95 - 7.06 (m, 1H), 7.11 - 7.22 (m, 2H), 7.35 (dt, J=5.9, 7.9 Hz, 1H)

## Example 10

2-[4-(2,3-Difluorobenzyl)phenoxy]-5-ethoxyaniline hydrochloride

5 [0066]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 200 MHz) δ (ppm); 1.31 (t, J=7 Hz, 3H), 3.97 (q, J=7 Hz, 2H), 5.17 (s, 2H), 6.65 (dd, J=3, 9 Hz, 1H), 6.79 (d, J=9 Hz, 1H), 6.91 (d, J=3 Hz, 1H), 6.98 (d, J=9 Hz, 2H), 7.07 (d, J=9 Hz, 2H), 7.21 - 7.53 (m, 3H)

## 10 Example 11

2-[4-(2,4-Difluorobenzyl)phenoxy]-5-ethoxyaniline hydrochloride

15 [0067]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 200 MHz) δ (ppm); 1.30 (t, J=7 Hz, 3H), 3.96 (q, J=7 Hz, 2H), 5.07 (s, 2H), 6.60 (dd, J=3, 9 Hz, 1H), 6.77 (d, J=9 Hz, 1H), 6.83 (d, J=3 Hz, 1H), 6.95 (d, J=9 Hz, 2H), 7.05 (d, J=9 Hz, 2H), 7.14 (dt, J=3, 7 Hz, 1H), 7.32 (dt, J=3, 9 Hz, 1H), 7.63 (dt, J=7, 9 Hz, 1H)

## 20 Example 12

2-[4-(3,4-Difluorobenzyl)phenoxy]-5-ethoxyaniline hydrochloride

25 [0068]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 200 MHz) δ (ppm); 1.30 (t, J=6 Hz, 3H), 3.96 (q, J=6 Hz, 2H), 5.04 (s, 1H), 6.47 - 6.56 (m, 1H), 6.70 - 6.78 (m, 2H), 6.97 (d, J=7 Hz, 2H), 7.02 (d, J=7 Hz, 2H), 7.26 - 7.36 (m, 1H), 7.39 - 7.59 (m, 2H)

## Example 13

30

2-[4-(3,5-Difluorobenzyl)phenoxy]-5-ethoxyaniline hydrochloride

[0069]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 200 MHz) δ (ppm); 1.29 (t, J=7 Hz, 3H), 3.95 (q, J=7 Hz, 2H), 5.11 (s, 2H), 6.42 - 6.58 (m, 1H), 6.65 - 6.83 (m, 2H), 6.95 (d, J=7 Hz, 2H), 7.00 - 7.05 (m, 3H), 7.15 - 7.28 (m, 3H)

## Example 14

40 2-[4-(2,5-Difluorobenzyl)phenoxy]-5-isopropoxylaniline hydrochloride

[0070]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 200 MHz) δ (ppm); 1.24 (d, J=6 Hz, 6H), 4.48 (sext, J=6 Hz, 1H), 5.10 (s, 2H), 6.58 (dd, J=3, 9 Hz, 1H), 6.76 (d, J=9 Hz, 1H), 6.81 (d, J=3Hz, 1H), 6.96 (d, J=9 Hz, 2H), 7.07 (d, J=9 Hz, 2H), 7.20 - 7.47 (m, 3H)

## Example 15

50

2-[4-(3-Nitrobenzyl)phenoxy]aniline hydrochloride

[0071]

(1) To a solution of 4-(2-nitrophenoxy)phenol (1.00 g, 4.3 mmol) in ethanol (50 ml) were added an iron powder (1.21 g, 0.022 g-atom) and a solution of ammonium chloride (0.14 g, 2.6 mmol) in water (10 ml), followed by reflux for 2 hours. The insoluble matter was filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, and after drying, the solvent was evaporated under reduced pressure to give 4-(2-aminophenoxy)phenol (0.85 g).

(2) To a solution of 4-(2-aminophenoxy)phenol (0.85 g, 4.2 mmol) in N,N-dimethylformamide (20 ml) were added 3-

nitrobenzyl chloride (0.87 g, 5.1 mmol), potassium iodide (0.70 g, 4.2 mmol) and potassium carbonate (0.88 g, 6.4 mmol), followed by stirring at 50°C for 3 hours. The reaction solution was poured into water and extracted with ethyl acetate, and the organic layer was washed with water and a saturated aqueous sodium chloride solution. After drying, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent; chloroform) to give 2-[4-(3-nitrobenzyloxy)phenoxy]aniline (0.64 g).

(3) 2-[4-(3-Nitrobenzyloxy)phenoxy]aniline (0.64 g, 1.9 mmol) was dissolved in ethyl acetate (10 ml), and 4 N hydrogen chloride - ethyl acetate solution (1 ml) was added, followed by stirring for 30 minutes. The solvent was evaporated under reduced pressure, and the residue was crystallized from diethyl ether to give the title compound (0.55 g).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 200 MHz) δ (ppm); 4.52 (s, 2H), 6.50 - 6.67 (m, 3H), 6.75 - 6.87 (m, 5H), 7.63 (t, J=8 Hz, 1H), 7.65 (br, 3H), 7.83 (d, J=8 Hz, 1H), 8.11 (d, J=8 Hz, 1H), 8.24 (s, 1H)

#### Example 16

##### 2-[4-(2-Fluorobenzyloxy)phenoxy]aniline hydrochloride

[0072]

(1) To a solution of 4-(2-nitrophenoxy)phenol (462 mg, 2.0 mmol) in N,N-dimethylformamide (20 ml) were added 2-fluorobenzyl bromide (400 mg, 2.1 mmol), potassium iodide (40 mg, 0.24 mmol) and potassium carbonate (300 mg, 2.2 mmol), followed by stirring at 50°C for 4 hours. The reaction solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution and dried. The solvent was evaporated under reduced pressure to give 1-[4-(2-fluorobenzyloxy)phenoxy]-2-nitrobenzene (0.65 g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz) δ (ppm); 5.13 (s, 2H), 6.93 (d, J=9 Hz, 1H), 7.01 (s, 4H), 7.05 - 7.55 (m, 6H), 7.93 (d, J=8 Hz, 1H)

(2) To a solution of 1-[4-(2-fluorobenzyloxy)phenoxy]-2-nitrobenzene (0.65 g, 1.9 mmol) in ethanol (50 ml) were added an iron powder (0.53 g, 9.5 mg-atom) and a solution of ammonium chloride (0.06 g, 1.1 mmol) in water (10 ml), followed by reflux for 3 hours. The insoluble matter was removed by filtration, the solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. After drying, the solvent was again evaporated under reduced pressure, the residue was dissolved in a small amount of ethyl acetate, and 4 N hydrogen chloride - ethyl acetate solution (2 ml) was added, followed by stirring for 30 minutes. The solvent was evaporated under reduced pressure, and crystallization from diethyl ether gave the title compound (0.62 g).

m.p. 154 - 154.6°C.

#### Example 17

##### 2-[4-(2,5-Dichlorobenzyloxy)phenoxy]aniline hydrochloride

[0073] The title compound was obtained from 4-(2-nitrophenoxy)phenol and 2,5-dichlorobenzyl bromide in the same manner as in Example 16.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 200 MHz) δ (ppm); 5.14 (s, 2H), 6.80 (d, J=9 Hz, 1H), 7.05 - 7.19 (m, 6H), 7.40 (dd, J=2, 8 Hz, 1H), 7.49 (dd, J=2, 8 Hz, 1H), 7.58 (d, J=8 Hz, 1H), 7.70 (d, J=2 Hz, 1H)

#### Example 18

##### 2-[4-(2,5-Difluorobenzyloxy)phenoxy]-5-ethoxyaniline

[0074] To a solution of 5-ethoxy-2-(4-hydroxyphenoxy)aniline (3.68 g, 15 mmol) in N,N-dimethylformamide (50 ml) were added potassium tert-butoxide (2.02 g, 18 mmol) and 2,5-difluorobenzyl bromide (3.11 g, 15 mmol), followed by stirring at room temperature overnight. The reaction solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution, and after drying, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [eluent;

ethyl acetate - hexane (1:4)] to give the title compound (4.29 g).

m.p. 72 - 73.5°C.

5 Example 19

2-[4-(2,5-Difluorobenzyl)phenoxy]aniline

[0075] The title compound was obtained from 2-(4-hydroxyphenoxy)aniline and 2,5-difluorobenzyl bromide in the same manner as in Example 18.

m.p. 59.5 - 60.5°C.

Example 20

2-[4-(2,6-Difluorobenzyl)phenoxy]-5-ethoxyaniline

[0076] The title compound was obtained from 5-ethoxy-2-(4-hydroxyphenoxy)aniline and 2,6-difluorobenzyl bromide in the same manner as in Example 18.

m.p. 245 - 246°C.

Example 21

2-[4-(2,6-Difluorobenzyl)phenoxy]aniline

[0077] The title compound was obtained from 2-(4-hydroxyphenoxy)aniline and 2,6-difluorobenzyl bromide in the same manner as in Example 18.

m.p. 88 - 89°C.

Example 22

2-[4-(2,5-Difluorobenzyl)phenoxy]-5-methoxyaniline hydrochloride

[0078] 2-[4-(2,5-Difluorobenzyl)phenoxy]-5-methoxyaniline prepared from 2-(4-hydroxyphenoxy)-5-methoxyaniline and 2,5-difluorobenzyl bromide in the same manner as in Example 18 was dissolved in ethyl acetate, and allowed to form the hydrochloric acid salt with 4 N hydrogen chloride - ethyl acetate solution to give the title compound.

m.p. 203 - 204°C.

Example 23

2-[4-(2,6-Difluorobenzyl)phenoxy]-5-methoxyaniline hydrochloride

[0079] 2-[4-(2,6-Difluorobenzyl)phenoxy]-5-methoxyaniline prepared from 2-(4-hydroxyphenoxy)-5-methoxyaniline and 2,6-difluorobenzyl bromide in the same manner as in Example 18 was dissolved in ethyl acetate, and allowed to form the hydrochloric acid salt with 4 N hydrogen chloride - ethyl acetate solution to give the title compound.

m.p. 193 - 194°C.

Experiment 1

Inhibitory Action on a Na<sup>+</sup>/Ca<sup>2+</sup> Exchange System using Cardiac Sarcolemmal Vesicles

[0080] Sarcolemmal vesicles prepared from the removed dog ventricular muscles according to the method described in the literature (L. R. Jones, Methods, Enzymol., 1988, 157, pp. 85) were used.

[0081] A Na<sup>+</sup>/Ca<sup>2+</sup> exchange activity using the sarcolemmal vesicles was measured according to the method

described in the literature (K. D. Philipson, et al., J. Biol. Chem., 1980, 255, pp. 6880). First, the sarcolemmal vesicles were suspended in a sodium-containing solution [160 mM sodium chloride, 20 mM Tris-hydrochloric acid (pH 7.4)] to make up to a protein concentration of 1.5 mg/ml, and allowed to stand for an hour to load Na<sup>+</sup> in the sarcolemmal vesicles. To 2.5 µl of the sarcolemmal vesicles was added 125 µl of a [<sup>45</sup>Ca]-calcium chloride solution [20 µM [<sup>45</sup>Ca]-calcium chloride, 160 mM potassium chloride and 20 mM Mops-Tris (pH 7.4)], and after 10 seconds, 900 µl of an ice-cooled lanthanum chloride solution [10 mM lanthanum chloride, 160 mM potassium chloride and 20 mM Mops-Tris (pH 7.4)] was added. The sarcolemmal vesicles were recovered on a nitrocellulose filter by suction filtration and washed three times with 900 µl of a lanthanum chloride solution. The concentration of Ca<sup>2+</sup> uptake in the sarcolemmal vesicles was determined by measuring a <sup>45</sup>Ca radioactivity by a scintillator. In addition, a Na<sup>+</sup>/Ca<sup>2+</sup> exchange activity-independent Ca<sup>2+</sup> uptake in the sarcolemmal vesicles was determined by carrying out the same procedure using a potassium-containing solution [160 mM potassium chloride, 20 mM Tris-hydrochloric acid (pH 7.4)] instead of the sodium-containing solution.

[0082] The test compound was used as a dimethyl sulfoxide solution thereof, and its inhibitory effect was evaluated in comparison with the vehicle-treated group. The results are shown in Table 2.

15

20

25

30

Table 2

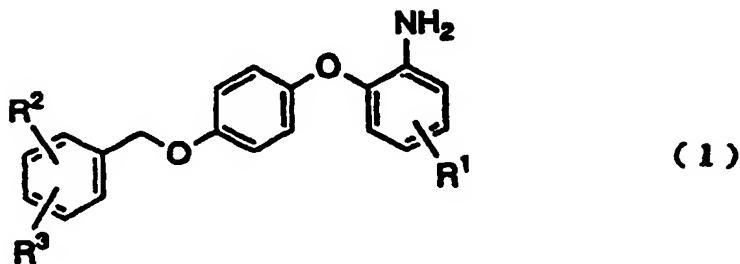
Compound Number	Na <sup>+</sup> /Ca <sup>2+</sup> exchange activity (% of control)
3	38
4	27
5	43
6	39
7	33
8	47
10	45

\*: The concentration of the test drug is 1 µM.

## Claims

35

1. A 2-phenoxyaniline derivative represented by Formula (1):



50       wherein R<sup>1</sup> is a hydrogen atom or a lower alkoxy group, R<sup>2</sup> is a halogen atom or a nitro group, and R<sup>3</sup> is a hydrogen atom or a halogen atom, or a pharmaceutically acceptable salt thereof.

55       2. The 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to Claim 1, wherein R<sup>1</sup> in Formula (1) is an ethoxy group or a propoxy group.

3. The 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to Claim 1, wherein R<sup>2</sup> and R<sup>3</sup> in Formula (1) are the same or different, and are each a halogen atom.

4. A pharmaceutical composition containing the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 as an effective component.
5. The 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 for use as a pharmaceutically active component.
6. An inhibitor of a  $\text{Na}^+/\text{Ca}^{2+}$  exchange system containing the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 as an effective component.
10. 7. A pharmaceutical composition for the treatment or prevention of ischemic heart diseases, ischemic cerebral diseases or ischemic renal diseases containing the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 as an effective component.
15. 8. Use of the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 for the manufacture of a pharmaceutical composition for the treatment or prevention of ischemic heart diseases, ischemic cerebral diseases or ischemic renal diseases.
20. 9. A method for the treatment or prevention of ischemic heart diseases, ischemic cerebral diseases or ischemic renal diseases which comprises the step of administering a pharmacologically effective amount of the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 to a human.
25. 10. A pharmaceutical composition for the protection of cells during thrombolytic therapy, angioplasty, bypass operation of coronary artery or organ transplantation containing the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 as an effective component.
11. Use of the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 for the manufacture of a pharmaceutical composition for the protection of cells during thrombolytic therapy, angioplasty, bypass operation of coronary artery or organ transplantation.
30. 12. A method for the protection of cells during thrombolytic therapy, angioplasty, bypass operation of coronary artery or organ transplantation which comprises the step of administering a pharmacologically effective amount of the 2-phenoxyaniline derivative or the pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 to a human.

35

40

45

50

55

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP98/04729

**A. CLASSIFICATION OF SUBJECT MATTER**  
Int.C1' C07C217/90, A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
Int.C1' C07C217/90, A61K31/135

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAPLUS (STN), REGISTRY (STN)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	JP, 10-218844, A (Taisho Pharmaceutical Co., Ltd.), 18 August, 1998 (18. 08. 98) (Family: none)	1-8, 10-11
A	JP, 5-194400, A (Kumiai Chemical Industry Co., Ltd.), 3 August, 1993 (03. 08. 93) & WO, 95/01339, A1	1-3
A	JP, 7-41465, A (Sumitomo Pharmaceuticals Co., Ltd.), 10 February, 1995 (10. 02. 95) & EP, 626373, A1 & US, 5556860, A	4-8, 10-11

Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier document but published on or after the international filing date
"L"	document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reasons (as specified)
"O"	documents referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"Z"	document member of the same patent family

Date of the actual completion of the international search 2 December, 1998 (02. 12. 98)	Date of mailing of the international search report 15 December, 1998 (15. 12. 98)
--------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------

Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

## INTERNATIONAL SEARCH REPORT

International application No. PCT/JP98/04729
-------------------------------------------------

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 9, 12  
because they relate to subject matter not required to be searched by this Authority, namely:  
These claims relate to methods for treatment of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required, under the provisions of PCT Article 17 (2)(a)(i) and Rule 39.1(iv) of the Regulations under the PCT, to search.
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest  The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.